SYMPOSIUM REPORT

Fetal programming of autonomic and HPA function: do people who were small babies have enhanced stress responses?

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Studies in several species have demonstrated that an adverse early environment can influence the development of the autonomic nervous system and hypothalamic–pituitary–adrenal (HPA) axis. The autonomic nervous system and HPA axis are key components of the neuroendocrine response to stress and many of these animal models show altered biological responses to stress. Recent research now suggests that these processes operate in humans. An adverse early environment, as evidenced by reduced birth or infant weight, is associated with enhanced autonomic and HPA responses to experimental psychological stress. However, there appear to be marked sex differences in the mechanisms involved. Epidemiological studies demonstrate that physiological changes in these neuroendocrine systems may predispose to cardiovascular disease through their influence on risk factors such as plasma glucose and lipid concentrations and blood pressure. Thus the combination of enhanced stress susceptibility and the psychosocial stressors to which people are exposed may be an important component of the disease risk in human populations.

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Studies in a wide range of species show that the set-point of the major hormonal systems which mediate the stress response (including the autonomic nervous system and hypothalamic–pituitary–adrenal (HPA) axis) can be altered during early life. This phenomenon has been most studied with respect to the HPA axis, which can be altered or 'programmed' prenatally by nutrient restriction, maternal adversity or exposure to synthetic glucocorticoids, and postnatally by neonatal handling, maternal deprivation or infection. (Matthews, 2002) The mechanisms underlying this phenomenon are thought to involve long-term changes in the expression of steroid receptors within the limbic system resulting from gene methylation (Weaver *et al.* 2004). As the function of these neuroendocrine systems is closely integrated with behavioural responses, it is not surprising that there is also evidence that behaviour can be programmed during development (Weinstock, 2001).

It has been suggested that this process is beneficial from an evolutionary perspective as it allows adaptation of organisms to their expected postnatal environments within a single generation (Gluckman & Hanson, 2004). In contrast, genetic adaptation in response to environmental pressures would take much longer to influence survival characteristics. The advantages of such a system are obvious. If a pregnant animal is exposed to a hostile environment with, for example, increased competition for food supplies or a high risk of predation, it is sensible that the development of the offspring be adapted for that environment. These adaptations might include increased levels of aggression or vigilance coupled with appropriate cardiovascular and metabolic responses which would enhance survival in such an environment. The evidence presented in this review suggests that similar processes may occur in humans. Although these are probably of little survival value in our modern society, they may have considerable clinical importance because of increasing evidence that they predispose to the development of a wide range of pathologies in adult life, including the metabolic

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syndrome and vascular disease, and may even influence behaviour.

Fetal programming of the autonomic nervous system and HPA axis in humans

Human studies are usually handicapped because of a lack of good markers of the fetal or early postnatal environment. However, in recent years birth weight or other anthropometric measurements obtained at birth or postnatally have been used as a proxy for an adverse fetal and infant environment. Clearly these measurements have severe limitations because of the many factors which are known to influence early growth. Nevertheless, an increasing body of data suggests that low birth weight is associated with alterations in the autonomic nervous system and HPA axis. Low birth weight babies have raised cortisol concentrations in umbilical cord blood and raised urinary cortisol excretion in childhood (Economides *et al.* 1988; Clark *et al.* 1996). They also have increased heart rate and reduced heart rate variability (indices of autonomic activity) when compared with controls during sleep (Spassov *et al.* 1994). A number of studies suggest that low birth weight is related to an increased resting pulse rate and fasting plasma cortisol concentrations in adulthood too (Phillips & Barker, 1997; Phillips *et al.* 1998). In the UK Hertfordshire Cohort Study, fasting plasma cortisol concentrations decreased linearly from 408 nmol l^{-1} in those who weighed 5.5 lb (2.5 kg) or less to 309 nmol l^{-1} among those who weighed 9.5 lb (4.3 kg) or more (Fig. 1). This trend was independent of the levels of corticosteroid binding globulin and was evident in the concentrations of biologically active, free cortisol. Although a single fasting cortisol measurement has substantial limitations, this observation suggested the possibility of an important link between birth size and adrenocortical hormone activity in adult life. This finding was also reported in population samples of 20-year-old-men and women born in Adelaide, South Australia, and 50-year-old-men and women born in Preston, UK (Phillips *et al.* 2000). A study of a subset of 205 men showed that those with lower birth weight had enhanced responses of plasma cortisol to $ACTH_{1\text{-}24}$ (Reynolds *et al.* 2001), with similar findings in a parallel study carried out in South Africa (Levitt *et al.* 2000).

The secretion of cortisol in the unstressed state does not appear to be related to birth weight (Fall *et al.* 2002; Kajantie *et al.* 2004). In addition, studies of HPA function based on the HPA responsiveness to corticosteroid releasing hormone (CRH) tests suggest that central regulation of the HPA axis is not disturbed in people who were small at birth (Ward *et al.* 2004*b*). Together these studies suggested that the previously observed relationship between birth weight and morning cortisol concentrations might represent a stress response due to the combination of fasting and the novel clinic setting in which the blood samples were obtained. As a consequence a number of studies were initiated to evaluate whether small size at birth is associated with an enhanced biological response to stress. These studies are now yielding intriguing results.

In a large cohort of Swedish army recruits, Nilsson and colleagues reported that there was a continuous relationship between size at birth and stress susceptibility

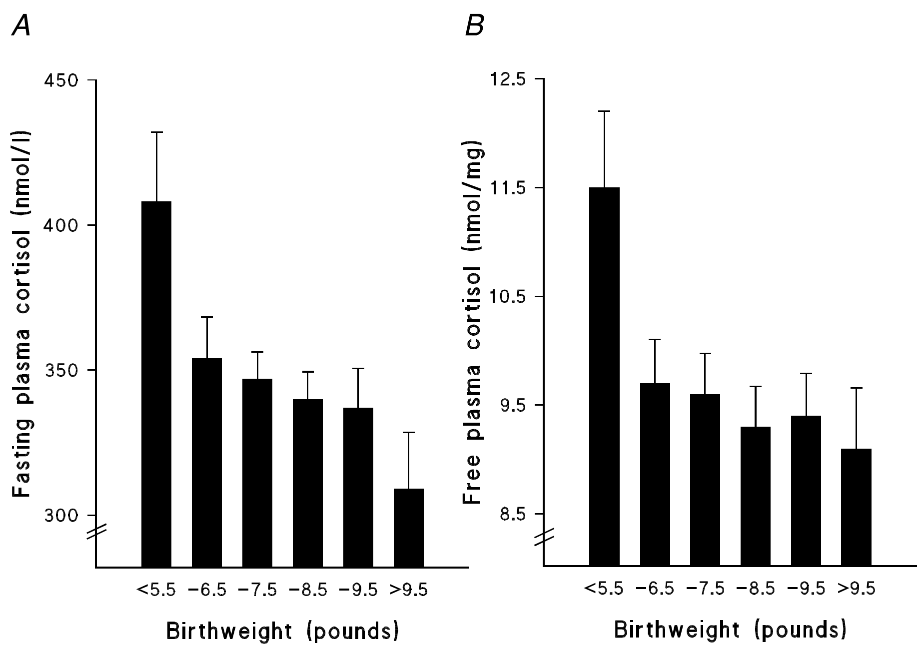

Figure 1. Mean fasting total cortisol concentrations (*A*) and estimated free cortisol concentrations (*B*) in 370 men aged 65 from the Hertfordshire Cohort Study according to birthweight

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in a psychological assessment of suitability for military combat duties (Nilsson *et al.* 2001). These results are supported by a study of 106 young healthy males who were exposed to the Trier Social Stress Test: a psychological stress test involving a public speaking task (Wust *et al.* 2005). Cortisol responses to the stress exposure were significantly and inversely related to the subjects' birth weight. In a recent study, Ward *et al.* (2004*a*) demonstrated that low birth weight is associated with enhanced blood pressure and heart rate responses to psychological stressors in women but not men. Further analyses of the data were carried out using spectral analysis techniques and autoregressive estimation of baroreflex function (a primary controller of blood pressure). This suggested that birth weight was associated with modulation of both sympathetic and parasympathetic function (Jones *et al.* 2005*b*). It also provided the first human evidence of a relationship between size at birth and altered baroreflex function. The findings of these studies suggested that there were marked sex differences in the nature of the relationship between size at birth and the stress response.

We have recently carried out a study of young children born in Southampton, who formed part of a prospective study of mothers and babies born at the Princess Ann Hospital, Southampton. The psychological test used was the Trier Social Stress Test adapted for children, which has been shown to give good adrenocortical responses. In this test, children are asked to perform a public speaking task involving storytelling and mental arithmetic for a panel of three unknown adult 'judges'. We measured changes in salivary cortisol secretion and assessed autonomic function with a BIOPAC, which records pulse and blood pressure changes, the ECG and cardiac impedance from which a variety of indices of autonomic function can be obtained. In a cross-sectional study of 68 boys and 72 girls (aged 7–9 years) there were again marked sex differences. In boys, markers of fetal growth restriction, such as low birth weight, were associated with raised arterial pressure and systemic vascular resistance, particularly following the stress test. In contrast, girls who were small at birth showed no such associations, but did show greater cardiac sympathetic nervous system activation as indicated by measures of pre-ejection period and corrected QT interval, both at rest and during stress (Jones *et al.* 2005*a*). Salivary cortisol responses were related to birth weight, head circumference and ponderal index at birth in boys but again not in girls (Jones *et al.* 2005*c*). These findings appeared to be independent of possible confounding factors such as obesity, education or social class.

The available data therefore suggest that there are marked sex differences in the relationship between birth weight and the stress response, with boys who are small at birth having an enhanced HPA and girls a predominantly sympathoadrenal response. This observation is supported by increasing animal evidence that fetal programming of the HPA axis differs by sex (Welberg & Seckl, 2001). Hippocampal corticosteroid receptor populations, which exert negative feedback on the HPA axis, are a possible factor in these sex differences. In animal experiments, receptor numbers are modified persistently by prenatal stress and the pattern and extent of this modification is sex-specific.

Although animal evidence suggests that changes in these neuroendocrine systems are closely integrated with behavioural responses, until recently there has been little information as to whether the early environment is associated with altered behaviour in humans. It is therefore of great interest that two recent studies reported at the Toronto DOHaD congress that low birth weight was associated with features of hyperactivity and reduced attention and that this effect was observed across the range of birth weights (Lahti *et al.* 2005; Schlotz *et al.* 2005).

The autonomic nervous system, the HPA axis and human pathology

Per Bjorntorp was among the first to suggest that a neuroendocrine disturbance involving the HPA axis may play an important part in the causation of the metabolic syndrome (Rosmond *et al.* 1998). As patients with Cushing's syndrome develop a severe form of the metabolic syndrome with hypertension, insulin resistance, glucose intolerance, dyslipidaemia, and central obesity, it is an attractive idea that less profound disturbances of the HPA might underlie the metabolic syndrome. Case $\times$ control and cross-sectional studies of people without pituitary or adrenal disease show that elevated plasma cortisol concentrations in morning samples are associated with high blood pressure, glucose intolerance, insulin resistance, hyperlipidaemia and possibly coronary artery disease (Smith *et al.* 2005). An increasing body of evidence also suggests that physiological alterations in autonomic responses are also important. For example, responsiveness to stressors which predominantly involve sympathetic activation is associated with carotid atherosclerosis (Everson *et al.* 1997), increased left ventricular mass (Allen *et al.* 1997) and in follow-up studies, with subsequent blood pressure and the prevalence of hypertension (Matthews *et al.* 2004).

It has increasingly been recognized that activation of these biological stress-response mediators might provide an explanation for the well-described link between psychosocial factors and ill-health. Although there is evidence that markers of psychosocial stress such as lack of control, job strain and poor self-esteem are linked with blood pressure and the progression of atherosclerosis (Brunner, 1997), the evidence has not been consistent. A major problem is the substantial individual differences

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in the biological response to the same external stressor. The evidence that the early environment has profound influences on the biological response to stress in later life may help resolve these difficulties in disentangling the relationships between stress and human disease. The combination of stress susceptibility and the psychological and social stressors that people are exposed to may be an important component in human disease risk.

In animal models changes in the activity of the HPA and autonomic nervous systems are linked with alterations in behaviour. Yet, remarkably little is known about this in humans despite extensive documentation in animal models (Weinstock, 2001; Kapoor & Matthews, 2005). As with the autonomic and neuroendocrine systems, behavioural changes, for example excessive shyness or aggression, may be disadvantageous in the present day social environment and may even contribute to the metabolic syndrome.

Implications and future directions

Despite the wealth of animal data, neuroendocrine programming in humans has been largely neglected. The mechanisms involved are clearly complex and hard to disentangle. For example, the effects of stressful influences on the mother are complex and are likely to be conditioned by other factors such as the maternal social environment, the fetal and maternal genetic backgrounds, the maternal early environment, and transgenerational effects. However, neuroendocrine programming may be a common pathway by which a wide variety of adverse external influences have long-term effects on the fetus (Fig. 2). These influences include psychosocial stress, ergonomic challenges (for example prolonged standing or carrying heavy loads), maternal diet (macro- and micronutrient intakes, dietary balance), the physical environment (heat or cold), exposure to environmental toxins or drugs, and maternal illness. It is likely that maternal stressors affect the fetus by the transplacental passage of maternal hormones such as cortisol. The human fetal HPA axis is well developed and functional in late gestation and able to respond to external factors, especially hypoxia and nutrient restriction. Therefore, external factors that reduce uterine blood flow would restrict fetal nutrient or oxygen supply and may initiate a fetal stress response. Examples of these are likely to be ergonomic factors such as prolonged standing or carrying heavy loads or the release of maternal stress hormones that in turn reduce uterine vascular perfusion. In the human context, maternal stress may also affect the fetus by influencing maternal behaviours. These include maternal self-medication, smoking and consumption of alcohol. Finally, it is also possible that external stressors such as trauma and noise which are perceived by the fetus could directly affect fetal stress responses.

The effects of stressors in the neonatal period and infancy and the extent to which the neonate or infant responds to stressors are poorly understood. Yet the large body of data from animal studies in a variety of species from rodent to non-human primates suggests that external stressors at this time have the potential for long-term, important effects. Neonatal vulnerability to stress is likely to be enhanced by factors such as prematurity, multiple birth, maternal parity, mode of delivery and low birth weight. These factors would be expected to increase the susceptibility to identifiable stressors such as cold, trauma and surgery, illness, antigenic challenge and difficulties in establishing feeding (breast or artificial).

Physiological studies to investigate these effects may importantly inform interventions both at the public health and individual levels. We still know remarkably little about how to optimize the environment of the mother. A number of studies have now been set up to evaluate the effects of dietary macronutrient and micronutrient

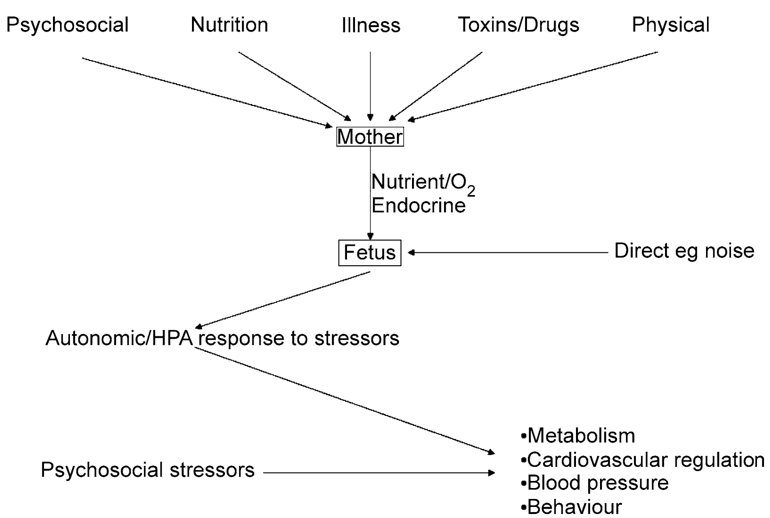

Figure 2. A variety of stressors experienced during pregnancy may result in lifelong alterations in autonomic and HPA axis activity in the developing fetus
In combination with adult psychosocial stressors, these may predispose to metabolic and cardiovascular disease.

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composition on the development of the infant. Fewer, however, are considering the wider environment of the mother and infant, for example the long-term effects of psychosocial stress or the ergonomic conditions in a working mother. Information from these studies is likely to have an important impact in arriving at scientifically valid public health policy and the direction of government funding to improve maternal and infant health. At the individual level identification of the mechanisms involved is likely to have many benefits. This includes the identification of high risk groups who may respond to lifestyle interventions (for example obesity reduction), or the identification of pharmacological targets. To achieve all of this represents a formidable challenge to basic, clinical and population research, but the impact on health may be considerable.

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